焼灼範囲（参考：肝臓）

17GのCool-tip RFシステムシングルニードルは、症例の焼灼径にあわせ、Exposure size（下図、白色部）を1cm、2cm、3cmと選択できる。

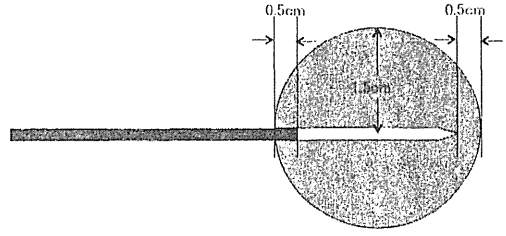

図３　ラジオ波焼灼療法による肝臓の焼灼範囲

ール）を注入してがんを殺傷するという経皮的な治療法の研究が進んでいました。エタノールに代わりマイクロ波、さらに出力の強いラジオ波が用いられるようになり、２００４年には公的医療保険の適応が認められ、今では標準治療の１つとして広く行われるようになりました。

　このラジオ波療法が乳がん治療の目的でわが国の医療施設に導入され始めてから、まだ10年も経っていないと思われます。ところが療法が広まるにつれ、ある〝異変〟が同時進行で進んでいったようなのです。

●治療後に異変が頻発

　２００４年～２００５年頃から、他の施設でラジオ波療法による乳がんの治療を受けて再発したという人の駆け込み受診が、全国のがん治療のセンター病院や基幹病院などで目立つようになってきたのです。

「その頃から私たちの施設でもそういう患者さんが顕著になりました」（木下外科長）

　そこで木下外科長らのグループはこの療法の適応を見極める必要がある、として国立がんセンター（現国立がん研究センター）の倫理委員会の承認を得て、２００６年６月より臨床研究を開始しました。

　ラジオ波療法後の再発の駆け込み受診が増えたのは、ラジオ波で焼き切ることのできない大きさの腫瘍、あるいは画像的には適応内と思われる大きさでも乳管内などに進展した旨に見えない広がりのある乳がんも治療対象として多く含まれていたのではないか、と推測されたからです。

　一般にラジオ波療法による焼灼範囲は電極から半径１・５cm、直径では最大３cmほどで、主病巣はこの範囲内でなければならないとされています（**図３**）。実際、肝がんの治療では大きさについては３cmまでの腫瘍がスタンダードな適応となっています。

　しかし、肝がんと違って乳がんの存在する乳房は、通電の抵抗がより強い脂肪組織が多いのです。先述したように乳管内を伝わって進展し、画像では確認しづらい広がりを持ったがんが存在することがあり、肝がんに対する適応基準を乳がんにそのまま流用していいか、疑念はあったものの当時ははっきりとわかっていなかったのです。

●２cmの腫瘍でも11％に焼き残しが……

　これらの事実を踏まえて、木下外科長らは乳がんに対する適応は３cmでは大きすぎる、それ以下だとしてもどれくらいの大きさまでを適応にすべきか、というテーマを設定して以下の方法で調べました。

「まずは超音波検査で２cm前後の大きさのがんを対象に、国立がん研究センターでラジオ波による治療を行った乳がん患者さんに対し、治療後、焼灼した部位およびその周囲組織を切除して、焼き残しがどれくらい含まれているか、検証したのです。趣旨を説明し了解を得て対象となった患者さんは50名でした」（木下外科長）

「その結果、電極を中心に紡錘型に焼灼範囲は及び、その中ではがんは完全に焼けることを確認しました。しかし焼灼範囲を超えると焼き残しが存在するようになり、２cm内の大きさの腫瘍でも約11％に焼き残しが見つかりました」

　この結果を踏まえ、木下外科長は、ラジオ波による乳がん治療の適応は、腫瘍（主病巣）の大きさを通常の超音波検査だけではなく、ＭＲＩ検査を加えて評価し、まずは大きさが１cm以内の腫瘍について、臨床試験を開始しました。

日本乳癌学会の実態調査が物語ること

　２０１０年には日本乳癌学会がラジオ波療法を含む３つの低侵襲療法の普及程度を調べる実態調査をしました。同学会の認定施設８３１施設にアンケート用紙を送付

し、５４７施設から回答を得ました。それによるとラジオ波療法は29施設が導入、合計１０４９の症例があり、そのうち約45％が臨床試験の目的で、約55％がそれ以外の目的で実施していたことがわかりました。

この結果を重視した日本乳癌学会は同年6月に「臨床試験以外の目的では行わないように」という趣旨の通知を会員に向けて出しました。

治療対象や治療効果、副作用の頻度、対処法などが十分に検証されておらず、「治療法としては確立されていないものを、それらを検証するための臨床試験以外の目的で行ってはならない」という意図を持って通達されたものと見てよいかと思います。

通達にある臨床研究以外の目的とは何を指すのかよくわかりませんが、たとえば自由診療（30数万円といった高額費用がかかるようです）などが入るのではないかと思われます。

通知に強制力はないものの、悪質なケースは対応を検討するという強いメッセージ性があり、通知を受けてこの療法を中止した医療施設もあります。

しかし継続している施設も依然として存在しています。またアンケート調査に回答をしてない医療施設もあって、ラジオ波療法をめぐる現場は混乱していると見なされても仕方がない現状があります。

強くこの療法を希望する場合は施設選びは慎重に

それでは現時点で、この療法を受けるとしたらどのような点に気をつけるべきでしょうか。

まず施設選びですが、3㎝以上の腫瘍や進行がんにまで適応を拡大している施設は論外といえるでしょう。木下外科長らのグループが行った臨床試験の結果を踏まえるなら、大きさが2㎝の腫瘍でさえ約10％の焼き残しがあるのですから、この点も踏まえた適応基準を示す施設が望ましいかもしれません。

患者さんが確認可能なわかりやすい目安としては、臨床試験目的でこの療法を行っているところが考えられます。療法のメリット・デメリットをきちんと説明してくれるはずだからです。とくに高度医療として厚生労働省の承認を得て実施している施設は、施設要件などの厳格な基準をパスしているため候補の筆頭になるのではないでしょうか。

そのリストは厚生労働省のサイトで調べることができます。現時点で国立がん研究センターなど7施設が載っています。

http://www.mhlw.go.jp/topics/bukyoku/isei/sensiniryo/kikan02.html

木下外科長はさらに、次のようなチェック項目を挙げます。

「腫瘍の大きさや形状を正確に診断するため、また治療後の経過を定期的に診ていくためにＭＲＩ画像による評価を行える施設。かつその評価を行える医師が存在することが第1（**写真4**）。第2に、焼灼後の針生検で採取した組織に生き延びたがん細胞が含まれているか、自前の検査組織（病理部）で評価できることが望まれます」（木下外科長）。

以上のように、乳がんに対するラジオ波療法はその適応基準、また治療効果の評価をいつどの時点でどの方法でするのか、といった重要な点が確立されていない現状があります。

だからこそ、この治療法を受けることを強く希望するのであれば、慎重に慎重を重ねるくらいの態度が必要です。

「これらの点がクリアされれば、ラジオ波療法は乳がんにおいても低侵襲のすぐれた治療法といえるようになるでしょう」（木下外科長）

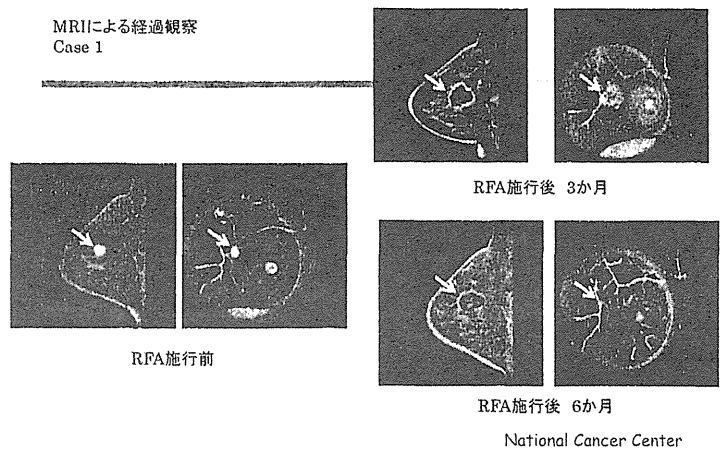

写真４　MRIによる経過観察

詳細な病理診断にて発見されるセンチネルリンパ節の微小な潜在的転移の予後に対する影響は，大きなものにはならない

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● Krag DN, *et al.*
Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: Overall survival findings from the NSABP B-32 randomised phase III trial.
Lancet Oncol.
2010; **11**: 927-933.

2010年にKrag DNらによりSLNBと腋窩リンパ節郭清との比較試験であるNSABP B-32試験の8年目の経過報告がなされた。OS, DFSの両者にて両群間に差が認められず早期乳癌に対するSLNBの妥当性が検証されつつある。SLNBの患者に対する恩恵から，長期的な結果を待たずに早期乳癌に対するSLNBはすでに標準治療となっている。

一方，SLNにおける組織切片の作成間隔や免疫組織染色の必要性などについては議論が多い。現在，リンパ節転移はその大きさにより大型転移（macrometastases：最大転移径2.0mm超），微小転移（micrometastases：最大転移径0.2～2.0mm），孤立性がん細胞（isolated tumor-cell clusters：最大転移径0.2mm以下）に分類される。したがって，大型転移を診断するためには少なくとも2mmの間隔で組織切片（slice section）を作成する必要があり，微小転移の診断には0.2mm（step section），孤立性がん細胞の診断にはそれ以上に細かい間隔で組織切片（serial section）を作成する必要がある。したがって，SLNの転移診断は病理医の業務を増やし，また施設間で格差が生じているのが現状である。はたして，詳細なSLNの病理診断は有用なのかとの疑問に答えたのが今回，紹介した論文である。免疫組織染色で診断されるリンパ節転移の大きさは平均0.1mmである。病理診断においてslice section以上の薄切や免疫組織染色を加えて微小転移や孤立性がん細胞を発見するのに労力を費やして，多くの潜在的転移を検出しても5年OSにおける絶対的な違いは1.2%と小さいため，通常の病理診断法で十分であろうという報告である。

今日では乳癌薬物療法の方針決定に際しては，腋窩リンパ節転移の有無ばかりでなく腫瘍本体の組織学的グレード，ホルモン感受性，human epidermal growth factor receptor 2（HER2）蛋白の発現なども考慮されることも関係している。2009年にはオランダのde Boer Mらが Micrometastases and Isolated Tumor Cells: Relevant and Robust or Rubbish?（MIRROR Study）でのレトロスペクティブな解析結果を報告している[1]。補助薬物療法の対象とならない比較的予後のよい早期乳癌においてSLNのisolated tumor-cell clusters, micrometastases群はn0群と比較して5年OSがともに劣ったと報告している。この研究ではSLNを150μm間隔にて詳細に検査している。

これら両方の報告から考察できることは，詳細な病理診断にて発見されるSLNの微小な潜在的転移の予後に対する影響は，補助薬物療法などの効果により大きなものにはならないということであろう。

REFERENCE

1) de Boer M, *et al.* Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med.* 2009; **361**: 653-663.

PROFILE

1988年慶應義塾大学医学部卒業．乳腺腫瘍外科の責任者としてセンチネルリンパ節生検をはじめ低侵襲外科治療の研究と開発に取り組んでいる．多施設共同研究にて実施されている高度医療評価制度下ラジオ波熱焼灼療法の研究責任者．

第Ⅲ相主試験における分子標的薬の重篤な薬物有害反応の報告について

Seruga B, Sterling L, Wang L, *et al.*
Reporting of serious adverse drug reactions of targeted anticancer agents in pivotal phase Ⅲ clinical trials.
J Clin Oncol. 2011; **29**: 174-185.

背景と研究目的

抗悪性腫瘍薬は，しばしば大規模ランダム化第Ⅲ相比較試験（randomized controlled trial；RCT）の結果，有用性が認められることによって承認される。専門家は，臨床試験で報告された薬剤の効果と毒性を勘案した上で有用性を判断するが，抗悪性腫瘍薬の毒性は時に臨床試験レベルでは十分に報告されていない。有害事象（adverse event；AE）と比較して，薬物有害反応（adverse drug reaction；ADR）は，開発中の薬剤が当該副作用の原因であることを強く疑わせる用語である。ほとんどのRCTでは，症例数が十分であり，通常観察されるAEを確認できるが，発現頻度がまれなAEや一定の潜伏期を経て出現するAEは，必ずしも十分に認識されない。RCTによっても報告されなかった重篤なADRが，市販後に明らかになるとの仮説を立て，米国で承認された分子標的薬について最新の添付文書に記載されているADRと大規模RCTで報告されたADRとを比較検討した。

方 法

米国食品医薬品局（FDA）のwebサイトより解析対象とする分子標的薬を選択した。すでに米国FDAで承認された分子標的薬の中で2008年と2009年に安全性に関する添付文書が改訂され，さらに少なくとも1報の大規模RCTが最新の添付文書に記載されている薬剤を選択条件とした。それぞれの薬剤について，死亡の可能性があるADRを含む「重篤なADR」とは，FDA labelの中で“warning/precaution”および“boxed warning”に記載されている事象とした。添付文書に引用されているRCTを解析し，論文中にこれらのADRが報告されているかどうかを検討した。

結 果

12種類の分子標的薬と最新の添付文書に記載されている36のRCTの論文を解析した。添付文書には，76種類の重篤なADRが記載され，その中で50%は潜在的に致死的であった。さらに重篤なADRの39%（30事象），致死的なADRの39%（15事象）が，発表論文に記載されておらず，さらにそれぞれ，49%と58%は，はじめの添付文書にも載っていなかった。論文に記載されていたADRとされていなかったADRを示す（表1）。“infusion reaction”，間質性肺炎，骨髄抑制，重篤な口内炎など多彩なADRがRCTでの論文では報告されていないことが判明した。

結 論

新規分子標的薬に関して，主要なRCTの報告論文や市販直後の添付文書では，重篤なADRについて限られた情報しか提供していない。まれではあるが，重篤なADRの情報は，対象患者に合併症や死亡を引き起こす可能性があり，実地医療の場においてこのような状況を理解しておくことは，重要である。

表1 ランダム化比較試験にて最も多く報告された薬物有害事象

重篤なADR	分子標的薬の数	少なくとも1報のRCTの論文でADRが報告されている分子標的薬	RCTの論文でADRが報告されなかった分子標的薬
心障害*	7	ボルテゾミブ，セツキシマブ，イマチニブ，ラパチニブ，リツキシマブ，スニチニブ，トラスツズマブ	—
infusion reaction	6	ベバシズマブ，セツキシマブ，パニツムマブ，リツキシマブ，トラスツズマブ	イブリツモマブ チウキセタン
間質性肺炎	6	エルロチニブ，トラスツズマブ	ボルテゾミブ，セツキシマブ，ラパチニブ，パニツムマブ
骨髄抑制	5	ボルテゾミブ，ダサチニブ，イブリツモマブ チウキセタン，イマチニブ	トラスツズマブ
重度の皮膚症状	5	セツキシマブ，パニツムマブ	エルロチニブ，イブリツモマブ チウキセタン，リツキシマブ
消化管穿孔	4	ベバシズマブ，エルロチニブ	イマチニブ，リツキシマブ
出血	4	ベバシズマブ，ダサチニブ，イマチニブ，スニチニブ	—
肝毒性	4	エルロチニブ，イマチニブ	ボルテゾミブ，ラパチニブ
脳障害†	3	NA	ベバシズマブ，ボルテゾミブ，リツキシマブ
QT間隔延長	3	NA	ダサチニブ，ラパチニブ，スニチニブ
腫瘍崩壊症候群	3	NA	ボルテゾミブ，イマチニブ，リツキシマブ
動脈血栓症	2	ベバシズマブ，エルロチニブ	—
体液貯留	2	ダサチニブ，イマチニブ	—
甲状腺機能低下症	2	スニチニブ	イマチニブ
腎不全	2	エルロチニブ，リツキシマブ	—
高血圧	2	ベバシズマブ，スニチニブ	—
低マグネシウム血症	2	セツキシマブ，パニツムマブ	—

ADR：薬物有害事象　RCT：ランダム化比較試験　NA：not available
＊左心室機能不全，うっ血性心不全，心突然死を含む。
† 可逆性後白質脳症症候群と進行性多巣性白質脳症を含む。

Seruga B, *et al. J Clin Oncol.* 2011; 29: 179.

●原　著●

乳癌薬物治療に伴う妊孕性への影響に関する情報提供の実態調査

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〔*Jpn J Cancer Chemother* **39**(3): 399-403, *March*, 2012〕

Survey on Oncologists-Provided Information on Treatment-Related Infertility to Breast Cancer Patients: Akiko Kubo[*1], Keiichi Koido[*1], Mari Sawada[*1], Yasuaki Ryushima[*1], Chikako Shimizu[*2], Tomoyasu Kato[*3], Masashi Ando[*2], Takayuki Kinoshita[*2], Koji Murakoshi[*1], Nobuaki Yokote[*1], Yasuhiro Fujiwara[*2] and Hiroshi Yamamoto[*1] (*[1]*Dept. of Pharmacy, *[2]*Dept. of Breast and Medical Oncology, and *[3]*Dept. of Gynecology, National Cancer Center Hospital*)

Summary

Purpose: Treatment-related infertility is an important issue facing breast cancer survivors of childbearing age. A previous study at the National Cancer Center Hospital between 2000 and 2004 analyzed 136 postoperative breast cancer patients under 40 years old, and found that only 7% of them had been provided with information on fertility-related issues by their treating physicians. However, the way in which information is shared may have changed, given the recent publication of national and international guidelines on fertility issues in cancer patients, and we hypothesized that there will be an increase in the percentage of cases in which information about fertility-related issues is provided. Methods: We retrospectively analyzed patients 40 years old or younger who underwent surgery for primary breast cancer in this hospital between 2007 and 2009. We assessed patients' and oncologists' backgrounds, pathological stage, treatment plans, and whether or not oncologists provided explanations regarding fertility-related issues. Results: One hundred cases were analyzed. Five percent, 15%, and 80% of patients were<30, 30-35, and>35 years old, respectively. Sixty-one percent of patients had partners, while 29% had prior deliveries. Information on fertility-related issues was provided to 56% of patients. Significant factors influencing whether information was provided were patients' reproductive history (odds ratio (OR): 5.717, 95% confidence interval (CI): 1.752-18.66, p=0.004) and recommended treatment (OR: 24.22, CI: 3.150-186.2, p=0.017). By contrast, oncologists' background (specialty, gender, and duration of career as a physician) was not significant. The frequency with which treatment plans were changed did not correlate statistically with the provision of information on fertility-related issues. Conclusions: Information on treatment-related infertility is now provided much more frequently than in the past. We should encourage both patients and medical professionals to increase their awareness about this important issue. **Key words**: Breast cancer, Chemotherapy, Infertility (*Receive May 13, 2011/Accepted Jul. 6, 2011*)

要旨　背景: 薬物治療に関連した不妊は挙児希望を有する乳癌患者にとって重要な問題である。国立がん研究センター中央病院（以下，当院）における2000～2004年を対象期間とした調査では，40歳以下の乳癌患者に術前・術後薬物療法が妊孕性に及ぼす影響が伝えられていたのは7%だった。今回，われわれは2007～2009年における情報提供の実態調査を行った。方法: 2007～2009年に当院で手術を受けた40歳以下の女性乳癌患者を対象とした。診療録から，妊孕性に関する医師からの情報提供の有無，患者および担当医師の社会的背景，治療レジメンを後方視的に調査した。結果: 対象患者は100名。年齢［<30歳/30～35歳/35歳≦］=［5/15/80］，病理病期［0/Ⅰ/Ⅱ/Ⅲ/Ⅳ］=［21/23/43/12/1］，パートナー［あり/なし］=［61/39］，出産歴［あり/なし］=［29/71］であった。情報提供［あり/なし］=［56/44］であった。情報提供の有無に影響する因子は，患者側の要因として出産歴（odds ratio (OR): 5.717, 95% CI: 1.752-18.66, p=0.004）や推奨される治療レジメン（OR: 24.22, 95% CI: 3.150-186.2, p=0.017）と関連がみられ，年齢やパートナーの有無は関連がみられなかった。また，医師側の背景因子（診療科，性別，医師経験年数）との関連はみられなかった。さらに，化学療法を含む治療方針からの変更割合は，情報提供の有無で差はみられなかった。結語: 2007～2009年においても，情報提供率は約60%にとどまり，癌治療に伴う妊孕性への影響について，医療者・患者双方の意識をさらに高める必要がある。

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はじめに

近年，診断技術や治療技術の進歩に伴い，がん患者の予後が改善されてきたことで，治療後のQOL向上が懸念されるようになった。その一つとして，治療に関連した不妊がある[1]。

乳癌の化学療法では卵巣機能障害が比較的高率に起きる。特にcyclophosphamide（CPA）は，治療後に永続的な無月経を惹起しやすい代表的な抗がん剤として報告されている[2]。乳癌は生殖年齢における罹患率が高く，挙児希望を有する乳癌患者にとって妊孕性への影響は重要な問題である。

2006年の米国臨床腫瘍学会（ASCO）の勧告では，医師は生殖能力を有する患者を治療する場合には，治療開始前に治療に伴う妊孕性の影響について十分に説明し，生殖医療の専門医への紹介を行うべきであるとしている。

しかし，国立がん研究センター中央病院（以下，当院）において2000～2004年を対象期間とした調査では，40歳以下の早期乳癌患者の術後補助療法を決定する際に，医師から患者に対し治療による妊孕性への影響について，積極的に説明が行われた頻度は7%にとどまった[3]。

本邦においても，2006年の日本乳癌学会の患者向けガイドラインに抗がん剤治療に伴う妊孕性への影響が明記される[4]など，患者を取り巻く情報環境に変化が現れはじめている。そこで今回，われわれは2006年以降における情報提供の実施状況の実態を明らかにするために調査・検討を行った。

Ⅰ．対象と方法

1．対象患者

2007年1月～2009年10月までの期間に当院乳腺外科で乳房切除術を施行した，手術時年齢が40歳以下の早期乳癌女性患者を対象とした。

2．調査方法および調査項目

調査は診療録を用いて後方視的に行った。調査項目は，妊孕性に関する情報提供の有無，対象患者における年齢，病理病期（pStage），パートナーの有無，出産歴の有無，医師から推奨された補助療法および実施された補助療法とした。なお，情報提供の有無はインフォームド・コンセント時の診療録に，不妊・早発閉経などの記載があった場合に，「情報提供あり」と判断した。

妊孕性に関する情報提供頻度の変化を調べるため，岡田らが報告した2000～2004年を対象期間とした症例をA群，今回調査を行った2007～2009年を対象期間とした症例をB群として比較を行った。患者背景における年齢の分類は，A群の調査に準じて行った。

情報提供の有無を決定する可能性のある背景因子として，患者側の要因（年齢，パートナーの有無，出産歴の有無，推奨された治療）および各対象患者における担当医師側の要因（診療科，性別および医師経験年数）の影響を検討した。

3．統計学的処理

2群間の比較にはχ^2検定を用いた。薬物治療に伴う妊孕性への影響に関する情報提供の有無にかかわる背景因子については，多重ロジスティック回帰分析により検討した。解析ソフトは，SPSS 15.0 J for Windowsを使用した。

Ⅱ．結　果

1．患者背景

B群の対象患者は100名であった。年齢中央値は37.5歳，年齢［<30歳/30～35歳/35歳≦］=［5/15/80］，パートナー［あり/なし］=［61/39］，出産歴［あり/なし］=［29/71］であった。情報提供［あり/なし］=［56/44］であった。また，術後に遠隔転移が発覚した患者（pStage Ⅳ）が1名認められた。

Table 1に両群の患者背景を示す。両群を比較すると，年齢層に差が認められ（p<0.0001），B群では35歳以上の患者が増加した。また，「出産歴あり」はA群が52.9%，B群が29%と有意に減少した（p=0.0002）。なお，pStage，パートナーの有無では両群間に有意な差は認めなかった。

2．妊孕性に関する情報提供の実施状況

担当医から患者に対し薬物治療に伴う妊孕性への影響に関する情報提供の実施頻度を示す（Fig. 1）。なお，B群で他の医療職種（看護師）から情報提供が行われていた症例が1例あったが，担当医からの説明の有無は不明であったため，「情報提供なし」と分類した。「情報提供あり」はA群が7%，B群が56%で8倍に増加した（p<0.0001）。

3．情報提供の有無に関連する背景因子

B群における情報提供の有無に関連する背景因子について解析した結果を示す（Table 2，3）。患者側の要因として，出産歴なし〔odds ratio（OR）: 5.717, 95% CI: 1.752-18.66〕と推奨補助療法がホルモン治療（OR: 9.436, 95% CI: 1.219-73.05），化学療法（OR: 24.22, 95% CI: 3.150-186.2）が有意なリスク因子であることが明らかとなった。患者の年齢やパートナーの有無は関連性がみられなかった（Table 2）。また，担当医師側の要因として，診療科，性別，医師経験年数はいずれも情報提供の有無に影響しなかった（Table 3）。これらの結果から，情報提供

Table 1　Patient characteristics

		Group A (2000-2004) n=136		Group B (2007-2009) n=100		p value (χ^2 test)
		n	%	n	%	
Age (years)	<30	13	9.6	5	5.0	<0.0001
	30~35	52	38.2	15	15.0	
	35<	72	52.9	80	80.0	
pStage	0	13	9.6	21	21.0	0.09
	I	27	19.9	23	23.0	
	II	73	53.7	43	43.0	
	III	23	16.9	12	12.0	
	IV	0	0	1	1.0	
Partner	Present	89	65.4	61	61.0	0.22
	Not present	47	34.6	39	39.0	
Prior delivery	Present	72	52.9	29	29.0	0.0002
	Not present	64	47.1	71	71.0	

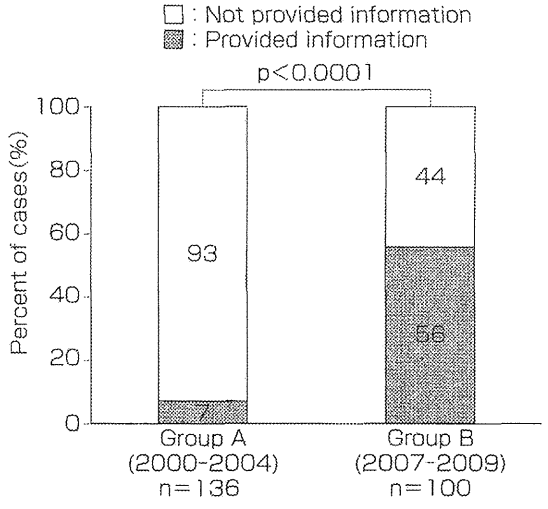

Fig. 1　The percentage of cases in which information on fertility-related issues was actively provided by treating physicians to primary breast cancer patients.
The percent of cases in which information was provided increased from 7 percent in Group A (2000-2004) to 56 percent in Group B (2007-2009).
p value: Chi square test

を「する」か「しない」かは，担当医師の背景に依存するのではなく，出産歴や提案する治療レジメンなどの患者背景に由来するものであることが示唆された。

4．補助療法の選択

医師が推奨した補助療法と，実際に実施された（≒患者が選択した）補助療法について示す（Table 4）。化学療法を含む治療から変更された割合は，「情報提供あり」群，「情報提供なし」群で差はみられなかった。つまり，妊孕性への影響に関して情報提供がされても治療方針の決定に影響がなかったことが示された。

Ⅲ．考　察

今回の調査結果から，2007年以降の症例において，医師から患者に対し妊孕性に関する情報提供が行われた頻度は56%と大幅に改善されていることがわかった。この理由として，2006年のASCOの勧告や日本乳癌学会の患者向けガイドラインの発表により，患者・医療者双方において，治療に伴う不妊のリスクに対する意識が高まった可能性がある。なお今回の調査は診療録を用いた後方視的調査であるため，診療録への記載不備などがあれば，結果に大きく影響する。つまり，以前よりも診療録への記載が徹底されるようになってきた可能性も考えられる。

両群の症例において，出産歴の有無が有意に異なるなど患者背景の違いが影響していることも考えられた。今回行った情報提供の有無に関連する背景因子の解析からは，出産歴のない患者に対してより積極的な情報提供が行われていることが示された。

また今回の検討では，不妊のリスクに関する情報提供の有無は，患者の治療選択に影響を与えなかった。しかし，情報提供は治療方針の内容にかかわらず，患者が納得して治療に取り組むために重要である。当院では薬剤師が患者指導に用いる術後化学療法のパンフレットに「卵巣機能障害」についての項目を作るなど，医師以外の医療職からも患者の潜在的なニーズを探りやすくするよう工夫している。

結論として，妊孕性に関する患者への情報提供は以前の調査よりも大幅に改善されていた。しかし，その割合は未だに約60%程度であり，妊娠可能年齢の全患者に対して情報提供が行われているわけではなく，医師は患者

Table 2 Background characteristics of Group B patients (2007-2009) who were or were not actively provided with information on fertility-related issues

		Physician actively provided information (n=56)		Physician did not actively provide information (n=44)		OR	95% CI	p value (χ^2 test)
		n	%	n	%			
Age (years)	Median	36.5		38				
	<30	4	7.1	1	2.3	1		0.063
	30~35	11	19.6	4	9.1	0.391	[0.022-0.693]	
	35<	41	73.2	39	88.6	0.092	[0.006-1.391]	
Partner	Present	34	60.7	27	61.4	1		0.152
	Not present	22	39.3	17	38.6	0.475	[0.171-1.317]	
Prior delivery	Present	11	19.6	18	40.9	1		0.004
	Not present	45	80.4	26	59.1	5.717	[1.752-18.66]	
Recommended adjuvant treatment	None	2	3.6	10	22.7	1		0.017
	Hormone therapy only	13	23.2	12	27.3	9.436	[1.219-73.05]	
	Treatment involving chemotherapy	36	64.3	22	50.0	24.22	[3.150-186.2]	
	Other (clinical trial)*	5	8.9	0	0	----	—	

OR: adjusted odds ratio, CI: confidence interval

*: Not applicable for calculating OR because all cases were provided with information on chemotherapy related-infertility

Table 3 Association between treating physicians' backgrounds and providing information on fertility-related issues

		OR	95% CI	p value (χ^2 test)
Specialty	Medical oncology (n=11)	1		0.269
	Breast surgery (n=5)	0.575	[0.216-1.534]	
Gender	Male (n=11)	1		0.684
	Female (n=5)	0.830	[0.339-2.033]	
Length of career	<15 years (n=9)	1		0.131
	≧15 years (n=7)	2.148	[0.796-5.792]	

OR: adjusted odds ratio, CI: confidence interval

Table 4 Patient selection of adjuvant treatment categorized by physician-provided information on fertility-related issues

	Physician actively provided information (n=56)		Physician did not actively provide information (n=44)	
	n	%	n	%
Treating physician's adjuvant treatment recommendation				
Chemotherapy-containing treatment	38	67.9	22	50.0
Patient's adjuvant treatment selection				
Chemotherapy-containing treatment	30	53.6	18	40.9

の背景に応じて選択的に情報提供を行っている可能性が示唆された。患者が納得して治療に取り組むためには，様々な状況を考慮しても情報提供は100%をめざすべきであると考える。癌治療に伴う妊孕性への影響について，医療者・患者双方の意識をさらに高められるよう働きかける必要がある。

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Randomized phase II study of three doses of oral TAS-108 in postmenopausal patients with metastatic breast cancer

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This randomized phase II study was intended to identify the optimal dose of TAS-108, a novel steroidal antiestrogen, for the treatment of breast cancer in postmenopausal Japanese women. The potential clinical effects of TAS-108 on the uterus, bone, serum lipids, and hormones were also investigated. Postmenopausal women with hormone receptor-positive metastatic breast cancer who had previously received one or two endocrine therapies were randomly assigned to one of the three possible dose levels of TAS-108 (40, 80 or 120 mg/day). Oral TAS-108 was given daily, and the efficacy and safety of the three doses were evaluated. A total of 97 patients (33, 32, and 32 in the 40-, 80-, and 120-mg groups, respectively) were treated with TAS-108. The clinical benefit rate was 30.3% for the 40-mg, 25.0% for the 80-mg, and 25.0% for the 120-mg group. The 40-mg group achieved the prespecified target threshold. TAS-108 at all dose levels was well tolerated and appeared to have no harmful effects in terms of the variables examined in this study. We conclude that the optimal dose of TAS-108 among the three doses is 40 mg, once daily, for further studies. JAPIC Clinical Trials Information number: Japic CTI – 121754. (*Cancer Sci* 2012; 103: 1708–1713)

Aromatase inhibitors have been widely used as first-line endocrine therapeutic agents for postmenopausal patients with HR-positive breast cancer and also adjuvant therapy in postmenopausal women with early breast cancer.[1,2] However, tamoxifen showed equivalent disease-free survival compared with AIs in patients with low tumor values of Ki-67 in an adjuvant trial,[3] and it has also been reported that tamoxifen holds potential for sequential treatment of postmenopausal patients with MBC progressing after AI treatment.[4] Therefore, tamoxifen still remains an important treatment option in HR-positive breast cancer. However, due to its estrogen-like effects on the uterus, tamoxifen has been associated with the risk of developing endometrial cancer,[5] which has been an important motivating factor in the development of new types of antiestrogen with different pharmacologic profiles.

A novel steroidal antiestrogenic compound, TAS-108 binds strongly to ERα and ERβ with a mechanism of action unlike tamoxifen,[6] and in humans is mainly metabolized by CYP3A4 enzymes in the liver.[7] TAS-108 shows pure antagonistic activity as it blocked both the N-terminal AF-1 and C-terminal AF-2 transactivation functions of ERα, abolished the recruitment of co-activators, but promoted the recruitment of co-repressors and allowed normal DNA binding. Additionally, TAS-108 has shown antagonistic effects on a mutant ERα reported to have a tamoxifen-resistant phenotype and preliminarily shown to have antitumor activity against tamoxifen- and AI-resistant cell lines.[8] TAS-108 has also shown fewer estrogenic effects on the uterus than tamoxifen in animal models.[6] Furthermore, a preclinical study suggested possible positive effects of TAS-108 on BMD.[9]

Several phase I studies were carried out in the USA involving postmenopausal healthy women and MBC patients.[10,11] In these studies, TAS-108 was well tolerated at all doses of 40–160 mg, and showed possible antitumor activity.

Two phase I studies of TAS-108 in Japan in 12 postmenopausal healthy women[12] and 15 MBC patients,[13] involving doses of 40, 80, or 120 mg showed a favorable safety profile, and encouraging antitumor activity in the MBC group. However, these studies were not designed to establish the optimal dose of TAS-108.

The present multicenter study was carried out to evaluate both the efficacy and safety of three different TAS-108 doses, and subsequently to identify the optimal dose of TAS-108 for further studies in postmenopausal Japanese patients with MBC. Considering long-term use, especially in the adjuvant setting, the effect on aspects not directly related to cancer would be especially important for administration in postmenopausal women. We also investigated the potential clinical impact of TAS-108 on the uterus, bone, serum lipids, and hormones.

Patients and Methods

Study design and treatment. In this multicenter, randomized, non-blinded phase II study carried out in Japan, patients were randomly assigned to receive oral TAS-108 with a daily dose

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of either 40, 80 or 120 mg (in units of 40 mg tablets; Taiho Pharmaceutical, Tokyo, Japan) after the first daily meal for 24 weeks or until disease progression, development of unacceptable toxicity, or withdrawal of consent. Patients with favorable response (CR, PR, or SD) at 24 weeks could continue the treatment. Two stratification factors: response to prior endocrine treatment, and presence of visceral metastasis, were used to balance the patient populations among the three dose groups at randomization.

At baseline, a full medical history was taken and a physical examination carried out. Patients also underwent clinical laboratory tests, examination of vital signs, electrocardiogram, and PS evaluation. At 2 and 4 weeks after initiating drug intake, and subsequently every 4 weeks, evaluations were carried out, including physical examination, toxicity assessment, and clinical laboratory tests. Endometrial thickness was measured by transvaginal (transabdominal) ultrasonography at baseline and every 24 weeks during treatment. Lumbar spine (L2–L4) BMD was assessed by dual energy X-ray absorptiometry at baseline and after 24 weeks of treatment. Serum hormones (E2, FSH, prolactin, thyroid-stimulating hormone, cortisol, testosterone, and sex hormone-binding globulin), serum lipid (apolipoprotein A-I and B) and BMMs (serum osteocalcin and I-CTP) were assessed at baseline and at regular intervals (measured at SRL Medisearch, Tokyo, Japan). All blood tests including for serum lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), were carried out on specimens obtained before the first daily meal.

Eligibility criteria. Postmenopausal HR-positive women aged 20–80 years with histologically or cytologically proven, locally advanced or MBC, were eligible for the study if they appeared suitable for endocrine therapy. The postmenopausal status was defined as being amenorrheic for at least 1 year (for patients aged 50 years or over), being amenorrheic for at least 1 year and with both serum E2 and FSH levels in the postmenopausal range, or being amenorrheic due to radiotherapy for at least 3 months with both E2 and FSH levels in the postmenopausal range (for patients aged under 50 years). All patients had to have at least one progressive target lesion after one or two different endocrine therapies. Patients could have received one prior chemotherapy regimen, unless it had been given as the most recent prior treatment. Patients who had had only adjuvant endocrine therapy were eligible if they had relapsed during therapy or <6 months from the completion or discontinuation of the therapy. Other inclusion criteria included: adequate organ function; a predicted life expectancy of >3 months; PS of 2 or less on the Zubrod scale.

Patients were ineligible if they had allergies to steroid preparations; abnormal vaginal bleeding at the start of the treatment; past serious thromboembolism; current serious complication(s); active double cancer; inflammatory breast cancer, lung metastasis with cancer-related lymphangitis, brain metastasis with any symptoms, and widespread liver metastasis.

The study was approved by the institutional review board of each participating center. Written informed consent was obtained from all patients.

Efficacy and safety assessments. Tumor response assessments were carried out at baseline and at 8-week intervals. The response was assessed according to the Response Evaluation Criteria in Solid Tumors criteria.[14] For CR and PR, the response had to be confirmed more than 4 weeks after the first date when a response was documented. The efficacy results were reviewed and determined by the independent CEC. Retrospective analyses for the response to TAS-108 were carried out to explore the subgroup, including patients who had tamoxifen- or AI-resistant tumors, defined as patients who had: (i) previously failed to respond to the most recent prior treatment for advanced disease; (ii) progressed following response to treatment; and (iii) relapsed either on adjuvant therapy or within 6 months from the completion of adjuvant therapy. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

Statistical considerations. The primary end-point was the CBR at 24 weeks, defined as the percentage of eligible patients who achieved a CR, PR, or SD for at least 24 consecutive weeks. The secondary end-points included ORR (CR or PR) and TTP. The secondary end-points also included safety and effects on ET, BMD, BMMs, serum lipids, and hormone levels.

We considered 35% as a clinically meaningful CBR and that that would be the expected CBR of TAS-108 in the study population, whereas a 10% CBR would be considered poor and lacking promise for future development. Sample size was estimated to ensure both appropriate precision for CBR estimation in all evaluable patients and sufficient statistical power to reject the null hypothesis with adjusted significance level for multiple comparisons. At least a total of 84 evaluable patients, 28 in each dose group, were required to carry out binomial tests for $P_1 = 35\%$ and $P_0 = 10\%$ in each dose group with 2.5% family-wise one-sided type-I error level with 80% statistical power in each test. For CBR estimation in total, and assuming a 5% drop-out rate, a total of 96 patients, 32 in each dose group, were planned to be enrolled in the study.

The Kaplan–Meier method was used to estimate TTP, which was defined as the time from first drug administration to disease progression. The 98.3% exact binomial CI was estimated for CBR and ORR in each dose group.

In order to explore the potential clinical impact of TAS-108 on the uterus, bone, serum lipids, and hormones, we carried out non-parametric analysis. Bone mineral density and BMMs were assessed in patients with no bone metastasis at baseline. Because of uncertainty regarding the asymptotic normality of changes in variables, the Wilcoxon signed-rank test was used to assess the significance of changes from baseline within each dose group with a value <0.05 considered as statistically significant.

Results

Patient population. A total of 98 patients were enrolled at 34 centers in Japan (Appendix I). One patient randomized to the 120-mg group was censored and did not receive any TAS-108 treatment due to not having had endocrine therapy as the most recent prior treatment. The treated patient population therefore comprised 97 patients who were fully assessable for efficacy and safety; 33 in the 40-mg group, and 32 each in the 80-mg and 120-mg groups. The baseline characteristics of the patients were well balanced among the three dose groups (Table 1). The study population included 14 patients with metastatic disease refractory to prior tamoxifen treatment and 70 were refractory to prior AI treatment.

Efficacy. The CBR determined by CEC was 30.3% (98.3% CI, 13.3–52.4) in the 40-mg group, 25.0% (98.3% CI, 9.5–47.2) in the 80-mg group, and 25.0% (98.3% CI, 9.5–47.2) in the 120-mg group, respectively (Table 2). The 40-mg group exceeded the target threshold of 10% in its lower limit of CI. The CEC-determined ORR was 9.1% (98.3% CI, 1.3–27.9) in the 40-mg group, 9.4% (98.3% CI, 1.3–28.6) in the 80-mg group, and 6.3% (98.3% CI, 0.4–24.3) in the 120-mg group, respectively (Table 2). The median TTP was 4.6 months in the 40-mg group, 3.7 months in the 80-mg group, and 3.6 months in the 120-mg group (Table 2). The Kaplan–Meier curve of TTP is shown in Figure 1.

In the subgroup analysis of the patient population of tumor refractory to tamoxifen or AI, TAS-108 treatment produced a CBR of 28.6% and 27.1%, respectively (Table 3).

Table 1. Patient characteristics at baseline

Characteristics	Dose group			Total
	40 mg (*n* = 33)	80 mg (*n* = 32)	120 mg (*n* = 32)	(*n* = 97)
Median age, years (range)	63.0 (44–80)	63.0 (50–74)	58.5 (48–78)	62.0 (44–80)
Performance status, *n* (%)				
0	28 (85)	27 (84)	28 (88)	83 (86)
1	5 (15)	5 (16)	4 (13)	14 (14)
2	0 (0)	0 (0)	0 (0)	0 (0)
Body mass index (median), kg/m^2	23.2	23.0	22.1	22.7
Prior treatment, *n* (%)†				
Endocrine therapy regimens				
1	19 (58)	13 (41)	21 (66)	53 (55)
2	14 (42)	19 (59)	11 (34)	44 (45)
Chemotherapy regimens				
0	21 (64)	28 (88)	23 (72)	72 (74)
1	12 (36)	4 (13)	9 (28)	25 (26)
Sites of metastasis, *n* (%)				
Soft tissue	20 (61)	23 (72)	19 (59)	62 (64)
Bone	12 (36)	15 (47)	17 (53)	44 (45)
Visceral	23 (70)	23 (72)	23 (72)	69 (71)
Other	2 (6)	0 (0)	4 (13)	6 (6)
Receptor status, *n* (%)‡				
ER+/PgR+	22 (67)	20 (63)	19 (59)	61 (63)
ER+/PgR−	11 (33)	9 (28)	11 (34)	31 (32)
ER−/PgR+	0 (0)	2 (6)	1 (3)	3 (3)
ER−/PgR−	0 (0)	0 (0)	0 (0)	0 (0)
HER2+	4 (12)	4 (13)	7 (22)	15 (15)
HER2−	24 (73)	23 (72)	23 (72)	70 (72)
HER2 unknown	5 (15)	5 (16)	2 (6)	12 (12)
Disease-free interval, *n* (%)				
<2 years	5 (15)	5 (16)	5 (16)	15 (15)
≥2 years	21 (64)	22 (69)	17 (53)	60 (62)

†Counting a case treated with adjuvant endocrine therapy/chemotherapy as one regimen, if it had relapsed either during therapy or within 6 months of completion of therapy. ‡Hormone receptor status (estrogen receptor [ER]/progesterone receptor [PgR]) was determined by each study site.

Table 2. Efficacy results

	Dose group		
	40 mg (*n* = 33)	80 mg (*n* = 32)	120 mg (*n* = 32)
Response			
CBR, %	30.3	25.0	25.0
98.3% CI	13.3–52.4	9.5–47.2	9.5–47.2
ORR, %	9.1	9.4	6.3
98.3% CI	1.3–27.9	1.3–28.6	0.4–24.3
CR, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
PR, *n* (%)	3 (9.1)	3 (9.4)	2 (6.3)
SD ≥ 24 weeks, *n* (%)	7 (21.2)	5 (15.6)	6 (18.8)
SD < 24 weeks, *n* (%)	15 (45.5)	14 (43.8)	13 (40.6)
PD, *n* (%)	8 (24.2)	10 (31.3)	11 (34.4)
Time to progression, months			
Median	4.6	3.7	3.6
95% CI	3.6–5.4	2.1–5.7	1.9–5.6

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, objective tumor response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety. Most patients (72.2%) experienced drug-related AEs (definite, probable, possible) including hot flushes, hyperhidrosis, and nausea as non-hematological toxicities (Table 4). The most common was hot flush, reported by 22.7% of patients. A majority of these AEs observed were mild (grades 1–2) and there was no clear dose dependency regarding severity or frequency of AEs. Discontinuation due to TAS-108-related toxicity was rare (2/97; one patient with grade 3 hypoacusis and one patient with grade 3 dizziness in the 80-mg group). One patient in the 80-mg group had surgery for grade 3 cataracts in both eyes.

Exploratory analysis. Table 5 shows the results of analysis for each value. TAS-108 did not cause significant endometrial thickening (median baseline ET, 3.3 mm; 24 weeks ET, 4.0 mm; $n = 37$). No change was observed in median BMD (−0.30%; $n = 20$), serum I-CTP, and osteocalcin levels. The median triglyceride level decreased significantly from 104.0 to 86.0 mg/dL ($P < 0.0001$); there were no changes in other serum lipids. Increases in PRL, testosterone, and sex hormone-binding globulin levels were observed.

Discussion

This randomized phase II study was designed to evaluate the efficacy and safety of 40, 80, or 120 mg TAS-108 given orally once daily in postmenopausal patients previously treated with one or two regimens of endocrine treatment (with a maximum of one regimen of chemotherapy), with HR-positive MBC, particularly including prior AI- and/or tamoxifen-resistant disease.

As the first step toward the best dose selection, we sought to find the "active" dose level(s) among the three dose groups based on the analysis of the primary end-point. The tolerability at the active dose level(s) was subsequently assessed to achieve a relative balance between efficacy and toxicity of TAS-108. In consequence, it is found that the lower dose of 40 mg showed, numerically, the highest CBR (30.3%) at 24 weeks and met the targeted expectations for clinical activity. This finding suggests that the two higher doses might have been beyond the plateau phase of the dose–response curve and therefore had a potential "reverse dose–response" effect. The safety parameters were similar between the three doses. In addition, secondary efficacy analyses supported the choice because TAS-108 at a dose of 40 mg had similar but slightly higher antitumor activity than the two higher doses. The 40 mg dose of TAS-108 was therefore recommended for further controlled studies against current therapeutic standards. The results observed in this study were largely similar to those reported by Buzdar *et al.*[15]

With the widespread use of AIs in the adjuvant setting, several drugs have recently been reported to be potentially effective in the treatment for breast cancer patients following the failure of AI treatment. Subgroup analysis revealed that there is biological evidence for a CBR of 28.6% (tamoxifen refractory) and 27.1% (AI refractory), and this finding supports the concept that there may be no major cross-resistance between tamoxifen/AI and TAS-108. These encouraging results suggest that this drug can expand the choice of endocrine therapy for MBC patients in that population.

The safety profile of TAS-108 at all dose levels was favorable even when compared with the known safety profile of tamoxifen or other selective estrogen receptor modulators, which was similar to that in a phase I study by Saeki *et al.*[13] The frequent drug-related AEs were hot flush, hyperhidrosis, and nausea, which were of only mild severity (grade 1 or 2), and did not interfere with TAS-108 treatment. The frequency and severity of AEs did not appear to be related to the dose of TAS-108, which has been reported previously in a single-dose study and repeated-dose studies.[10–13] In the present study, grade 3 cataract was reported as a serious AE in one patient aged 63 years. Taking into account the report that tamoxifen can cause visual disorders, the relationship of the cataract to

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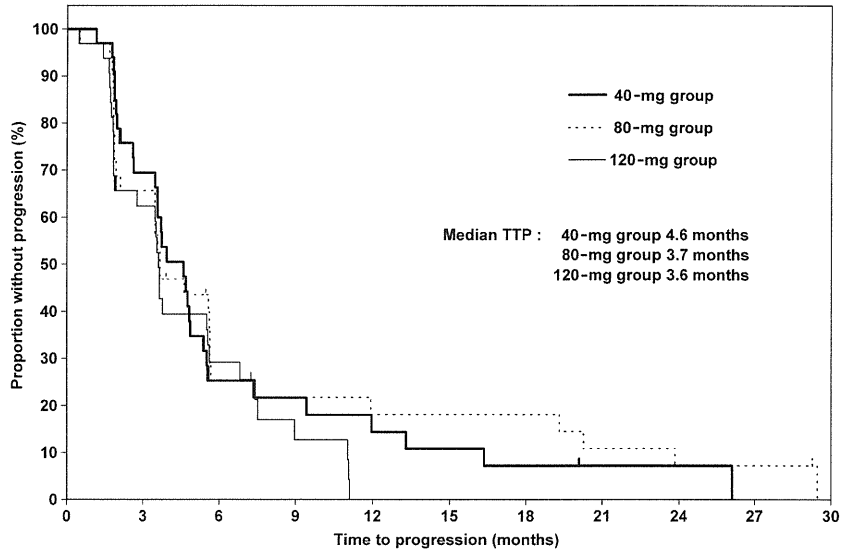

Fig. 1. Kaplan–Meier estimates for time to progression (TTP) in postmenopausal Japanese women with breast cancer treated with three different doses of TAS-108.

Table 3. Subgroup analysis for response to TAS-108 within each dose group (tumor refractory to prior tamoxifen and aromatase inhibitor treatment)

	Tamoxifen refractory (n = 14)	Aromatase inhibitor refractory (n = 70)
Clinical benefit rate (%)	28.6	27.1

TAS-108 was considered "possible". No other clinical observations associated with the significant side-effects of tamoxifen or AIs, such as thromboembolic events or bone fracture, have been reported. Therefore, the low toxicity profile of TAS-108, coupled with the evidence of activity in MBC patients, justifies further clinical testing.

To date, there is no apparent clinical evidence of a stimulating effect of TAS-108 on the endometrium in prior phase I studies involving Japanese and Caucasians patients,[11,13] and in the present exploratory analysis TAS-108 did not cause significant endometrial thickening. In this study, no change was observed in BMD or BMMs, unlike with tamoxifen. This observation suggests that TAS-108 may have few estrogenic effects on bone. Serum triglyceride was significantly decreased with no unfavorable changes in other cardiovascular risk factors tested in this study. TAS-108 had no significant clinical effect on hormones. We acknowledge that because this was not an adjuvant study, there were several limitations to this exploratory analysis, such as a reduction in the number of MBC patients due to withdrawal from this study, and a relatively short length of drug exposure (particularly for analysis of the uterus and bone). Therefore, the effects of TAS-108 on these values seemed tentative and need further investigation. However, the present analysis assessing the clinical potential impact of TAS-108 suggests that this drug may not negatively affect the safety profile of postmenopausal patients.

In conclusion, TAS-108 at the 40 mg dose level showed promising results regarding the primary end-point of this study, and it was well tolerated at all dose levels in postmenopausal Japanese patients who had received one or two previous endocrine therapies. Based on these results, we determined the optimal dose of oral TAS-108 to be 40 mg, once daily, for further clinical studies.

TAS-108, a novel steroidal antiestrogen, may have the potential to develop into a clinically useful second- or third-line endocrine therapy for HR-positive breast cancer refractory to AI and/or tamoxifen.

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Table 4. Drug-related adverse events occurred in >10% of postmenopausal Japanese women with breast cancer treated with TAS-108, in either dose group

Event†	Dose group						Total (n = 97)	
	40 mg (n = 33)		80 mg (n = 32)		120 mg (n = 32)			
	All grades, n (%)	Grades 3–5, n (%)	All grades, n (%)	Grades 3–5, n (%)	All grades, n (%)	Grades 3–5, n (%)	All grades, n (%)	Grades 3–5, n (%)
Hot flush	7 (21.2)	0 (0)	8 (25.0)	0 (0)	7 (21.9)	0 (0)	22 (22.7)	0 (0)
Hyperhidrosis	2 (6.1)	0 (0)	3 (9.4)	0 (0)	6 (18.8)	0 (0)	11 (11.3)	0 (0)
Nausea	1 (3.0)	0 (0)	3 (9.4)	0 (0)	5 (15.6)	0 (0)	9 (9.3)	0 (0)
Uterine leiomyoma	0 (0)	0 (0)	4 (12.5)	0 (0)	1 (3.1)	0 (0)	5 (5.2)	0 (0)
Blood cholesterol increased	4 (12.1)	0 (0)	1 (3.1)	0 (0)	0 (0)	0 (0)	5 (5.2)	0 (0)

†Patients could have had more than one event.

Table 5. Analysis of endometrial thickness (ET), bone mineral density (BMD), bone metabolism markers (BMMs), serum lipids, and endocrine hormones in postmenopausal Japanese women with breast cancer treated with TAS-108

Variable	*n*	Baseline (median)	8† or 24‡ weeks (median)	Change or percentage change§ from baseline to 8† or 24‡ weeks		
				Median	Range	*P*¶
ET, mm	37	3.30	4.00	0.00	−6.00–13.10	0.0850
BMD, g/cm^2	20	0.83	0.84	−0.30	−10.74–8.79	0.5220
BMMs						
Serum Osteocalcin, ng/mL	50	9.50	9.20	−0.62	−38.75–85.42	0.8420
Serum I-CTP, ng/mL	51	3.40	3.40	−3.03	−52.86–105.26	0.4120
Serum lipids						
Total-cho, mg/dL	93	208.00	212.00	0.00	−78.00–94.00	0.4410
HDL-cho, mg/dL	92	62.00	63.90	0.00	−28.00–51.00	0.1960
LDL-cho, mg/dL	91	121.00	127.00	3.00	−57.00–81.00	0.0830
Triglycerides, mg/dL	93	104.00	86.00	−13.00	−217.00–301.00	<0.0001
APO-A1, mg/dL	93	147.00	151.00	4.00	−45.00–59.00	0.1810
APO-B, mg/dL	93	99.00	99.00	1.00	−33.00–42.00	0.6680
Endocrine hormones						
E2, pg/mL	93	10.00	11.00	0.00	−11.00–33.00	0.1310
FSH, mIU/mL	93	44.49	44.80	−2.60	−24.27–26.88	0.3210
Prolactin, ng/mL	93	8.33	8.45	0.42	−41.12–40.79	0.0280
Testosterone, ng/dL	93	0.21	0.22	0.02	−0.23–0.31	0.0190
TSH, μIU/mL	93	2.58	2.51	0.00	−5.90–94.30	0.6350
Cortisol, μg/dL	93	13.60	13.20	0.20	−16.30–22.10	0.7540
SHBG, nmol/L	93	71.40	91.90	14.00	−110.00–133.40	<0.0001

†Bone metabolism markers, serum lipids, and endocrine hormones were assessed at the 8-week point in patients who received TAS-108 for 8 weeks or more. ‡Endometrial thickness and BMD were assessed at the 24-week point in patients who received TAS-108 for 24 weeks or more. §Data are presented as change from baseline, except BMD and BMMs as percentage change from baseline. ¶*P*-values based on the Wilcoxon signed-rank test. APO-A1, apolipoprotein A-I; APO-B, apolipoprotein B; HDL-cho, high-density lipoprotein cholesterol; I-CTP, cross-linked carboxy-terminal telopeptide of type I collagen; LDL-cho, low-density lipoprotein cholesterol; SHBG, sex hormone-binding globulin; Total-cho, total cholesterol; TSH, thyroid-stimulating hormone.

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Disclosure Statement

Hideo Inaji, Takahiro Nakayama, Naohito Yamamoto, Shigehira Saji, Toshiaki Saeki, and Shinzaburo Noguchi have received honoraria from Taiho Pharmaceuticals. Toshiaki Saeki and Shinzaburo Noguchi have received research funding from Taiho Pharmaceuticals. Tadashi Ikeda and Shinzaburo Noguchi have received consulting fees from Taiho Pharmaceuticals. The other authors have declared no conflicts of interest.

Abbreviations

AE	adverse event
AI	aromatase inhibitor
BMD	bone mineral density
BMM	bone metabolism marker
CBR	clinical benefit rate
CEC	Clinical Efficacy Committee
CI	confidence interval
CR	complete response
E2	17β-estradiol
ER	estrogen receptor
ET	endometrial thickness
FSH	follicle-stimulating hormone
HR	hormone receptor
I-CTP	cross-linked carboxy-terminal telopeptide of type I collagen
MBC	metastatic breast cancer
ORR	objective tumor response rate
PR	partial response
PS	performance status
SD	stable disease
TAS-108	(7α)-21-[4-[(diethylamino)methyl]-2-methoxyphenoxy]-7-methyl-19-norpregna-1,3,5(10)-trien-3-ol 2-hydroxy-1,2,3-propanetricarboxylate
TTP	time to progression

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Appendix I

The following institutions participated in this study: Hokkaido Cancer Center (Sapporo), Iwate Medical University (Morioka), Yamagata Prefectural Central Hospital (Yamagata), Tohoku University Hospital (Sendai), KKR Tohoku Kosai Hospital (Sendai), Tochigi Cancer Center (Utsunomiya), Saitama International Medical Center, Saitama Medical University (Hidaka), Saitama Red Cross Hospital (Saitama), Saitama Cancer Center (Ina), National Cancer Center Hospital (Tokyo), St. Luke's International Hospital (Tokyo), Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (Tokyo), Chiba Cancer Center (Chiba), Tokai University School of Medicine (Isehara), Kanagawa Cancer Center (Yokohama), Yokohama Municipal Citizen's Hospital (Yokohama), Kitasato University School of Medicine (Sagamihara), Niigata Cancer Center Hospital (Niigata), Seirei Hamamatsu General Hospital (Hamamatsu), Aichi Cancer Center (Nagoya), Nagoya Medical Center (Nagoya), Nagoya City University Graduate School of Medical Sciences (Nagoya), Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka), Graduate School of Medicine, Osaka University (Suita), Osaka National Hospital (Osaka), Osaka Kouseinenkin Hospital (Osaka), Sakai Municipal Hospital (Sakai), Kansai Rosai Hospital (Amagasaki), Hyogo Cancer Center (Akashi), Shikoku Cancer Center (Matsuyama), Hiroshima University Hospital (Hiroshima), Kurashiki Central Hospital (Kurashiki), Kyushu Cancer Center (Fukuoka), and Kumamoto Municipal Hospital (Kumamoto).

Randomized Phase II Study of Primary Systemic Chemotherapy and Trastuzumab for Operable HER2 Positive Breast Cancer

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Abstract

Primary systemic therapy for patients with HER2$^+$(human epidermal growth factor receptor 2 positive) breast cancer may be improved by adding trastuzumab to chemotherapy. This randomized phase II trial compared 2 chemotherapy regimens comprising FEC (5-fluorouracil/epirubicin/cyclophosphamide), trastuzumab and either PH (paclitaxel) or DH (docetaxel) in 102 patients. FEC-PH and FEC-DH achieved high pathologic complete response rates. Breast conserving surgery was possible in more patients in the paclitaxel arm.

Background: In primary systemic therapy in patients with human epidermal growth factor receptor 2 positive (HER2$^+$) breast cancer, improvements in pathologic complete response (pCR) rate have been achieved by administering trastuzumab. **Patients and Methods:** Patients with stage II or IIIA HER2$^+$ operable breast cancer were randomly assigned to receive four 3-weekly cycles of FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) followed by 4 cycles of 3-weekly trastuzumab (8 mg/kg week 1 and then 6 mg/kg) with either 12 weekly doses of paclitaxel 80 mg/m^2 (FEC-PH) or 4 cycles of 3-weekly docetaxel 75 mg/m^2 (FEC-DH). **Results:** Between March 2007 and June 2008, 102 patients were enrolled. Forty-nine patients receiving FEC-PH and 47 receiving FEC-DH were assessable for efficacy and safety. Eighty-four patients completed treatment and underwent surgery. There was no significant difference in the pCR rate between the 2 groups (46.9% [95% CI, 33.7%-60.6%] with FEC-PH vs. 42.6% [95% CI, 29.5%-56.8%] with FEC-DH; $P = .67$). Analysis by hormone receptor (HR) status showed pCR rates of 54.2% (32/59) in HR$^-$ tumors and 29.7% (11/37) in HR$^+$ tumors ($P = .02$). Among HR$^-$ tumors, the pCR rates were 65.4% and 45.5% in patients treated with FEC-PH and FEC-DH, respectively ($P = .13$). **Conclusions:** There was no significant difference in pCR rate between FEC-PH and FEC-DH. Both regimens achieved higher pCR rates in HR$^-$ than HR$^+$ breast cancer, and there was a trend toward higher pCR in HR$^-$ tumors with FEC-PH compared with FEC-DH. Further investigation is warranted to explore the relationship between efficacy and HR status.

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Introduction

Primary systemic therapy (PST) is regarded as one of the standard therapies for locally advanced breast cancer and selected patients with operable disease to facilitate breast conservation.[1-4] Patients achieving pathologic complete response (pCR) in the primary lesion and with no residual tumor in axillary nodes after PST have longer recurrence-free survival than those without pCR.[4-6] Consequently, pCR is commonly used as a surrogate for long-term outcome when evaluating novel chemotherapy regimens. Currently, sequential regimens, including an anthracycline followed by either weekly paclitaxel or 3-weekly docetaxel are commonly used to achieve high pCR rates.[3,7]

Trastuzumab plays an important role in therapy for human epidermal growth factor receptor 2 (HER2) positive ($HER2^+$) breast cancer, and its efficacy has been proven in both the adjuvant[8-10] and the metastatic[11,12] settings. In the neoadjuvant setting, improvements in the pCR rate have been achieved by administering trastuzumab with PST in patients with $HER2^+$ breast cancer. In a randomized trial that compared chemotherapy with or without trastuzumab, the trastuzumab-containing regimen improved the pCR rate (65.2% vs. 26.3%; $P = .002$).[13] A second randomized trial, the neoadjuvant herceptin (NOAH), showed a higher pCR rate with the combination of chemotherapy and trastuzumab than chemotherapy alone (39% vs. 20%; $P = .002$).[14] In addition, single-arm trials that evaluated the combination of chemotherapy and trastuzumab as PST showed high pCR rates.[15-20] Recently, it was reported that patients who achieve pCR have longer survival compared with those who do not achieve pCR, even in a $HER2^+$ population.[21,22] It is possible, therefore, that pCR could be considered to be a surrogate marker for the efficacy of PST, even in patients with $HER2^+$ breast cancer, although definitive evidence is required to confirm this proposition. Based on these data, we conducted a randomized phase II trial to compare pCR rates achieved with FEC (5-fluorouracil/epirubicin/cyclophosphamide) followed by weekly paclitaxel plus trastuzumab and FEC followed by 3-weekly docetaxel plus trastuzumab as PST for $HER2^+$ breast cancer.

Patients and Methods

Patient Eligibility

Eligible patients had previously untreated, unilateral, histologically confirmed, invasive, noninflammatory breast carcinoma. Histologic confirmation of invasive cancer was performed by core needle biopsy (CNB). $HER2^+$ was defined as a score of 3+ by immunohistochemistry or a HER2 gene copy-chromosome 17 ratio of ≥2.0 by fluorescence in situ hybridization. Patients with a tumor ≥2 cm at the largest dimension by ultrasonography or <2 cm with axillary lymph node metastasis clinically diagnosed as positive were eligible (clinical stage II and IIIA). Patients with axillary nodes enlarged by >1 cm at the largest dimension according to ultrasonography were considered node positive without the need for confirmatory biopsy. Patients with T4N3 (supraclavicular lymph node), or distant metastatic disease (M1) were excluded from the study.

Other requirements were age between 18 and 65 years, ECOG (Eastern Cooperative Oncology Group) performance status 0 to 2, adequate bone marrow function (absolute granulocyte count ≥1500/mm^3 and platelet count ≥100,000/mm^3), liver function (total bilirubin level ≤1.5 mg/dL and liver transaminase levels [aspartate aminotransferase and alanine aminotransferase] ≤60 IU/L), and renal function (serum creatinine level ≤1.5 mg/dL). Patients with a history of ischemic cardiac disease and cardiomyopathy or a left ventricular ejection fraction (LVEF) <60% according to echocardiogram were excluded. Patients with clinically negative axillary lymph nodes had the option of undergoing pretreatment sentinel lymph node biopsy (SLNB). The study was approved by institutional review boards and was conducted in accordance with the Declaration of Helsinki. All the patients provided written informed consent.

Study Design and Preoperative Systemic Therapy

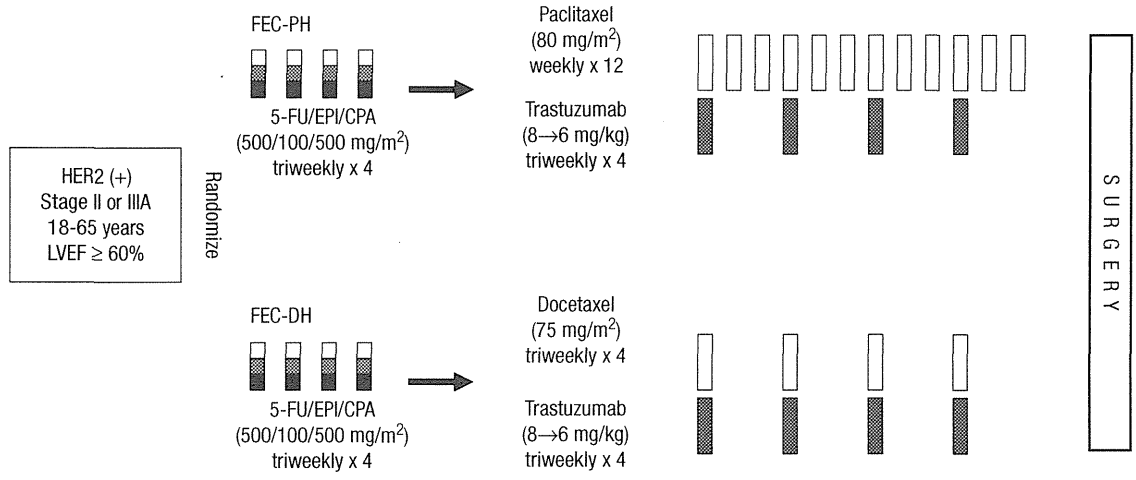
Patients were randomly assigned to receive either FEC followed by the combination of paclitaxel and trastuzumab (FEC-PH) or FEC followed by the combination of docetaxel and trastuzumab (FEC-DH). The dose and schedule of FEC and docetaxel were selected based on efficacy and safety data from our previously reported study of PST.[23,24] FEC consisted of 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 administered by intravenous (I.V.) infusion on day 1 every 3 weeks for 4 cycles (Figure 1). Paclitaxel was administered at 80 mg/m^2 I.V. over 1 hour on days 1, 8, and 15 every 3 weeks for 4 cycles. Docetaxel was administered at 75 mg/m^2 I.V. over 1 hour on day 1 every 3 weeks for 4 cycles. In both arms, trastuzumab was administered at a dose of 8 mg/kg I.V. over 90 minutes on day 1 of the first cycle and subsequent doses were administered at a dose of 6 mg/kg over 30 minutes every 3 weeks for a total of 4 cycles.

If a patient developed grade ≥3 febrile neutropenia, thrombocytopenia <25,000/mm^3, or grade ≥3 nonhematologic toxicity, then the doses of epirubicin and docetaxel were reduced by 25% and 20%, respectively, in subsequent cycles. The dose of paclitaxel was reduced by 25% in subsequent cycles if a patient developed grade 3 neurotoxicity. Before administration of the following cycle of FEC or docetaxel, the patients were required to have a granulocyte count ≥1500/mm^3, platelet count ≥75,000/mm^3, and no nonhematologic toxicity of grade >2 (excluding alopecia). Before administration of the next cycle of paclitaxel, the patients were required to have a granulocyte count ≥1000/mm^3, platelet count ≥75,000/mm^3, and no nonhematologic toxicity of grade >2 (excluding alopecia). If toxicity did not improve within 2 weeks, then chemotherapy and trastuzumab were discontinued and surgery was recommended.

Therapy After Preoperative Chemotherapy

Patients who were considered candidates for breast-conserving therapy (BCT) were offered lumpectomy. Patients who refused or were considered inappropriate for BCT received total mastectomy. Axillary lymph node dissection (AxLND) was mandatory, except in the patients diagnosed with nonmetastatic disease by SLNB before PST. Surgery was performed within 8 weeks after completion of preoperative chemotherapy. All the patients who underwent BCT received whole-breast irradiation. After completion of preoperative chemotherapy and surgery, the patients with hormone receptor (HR) positive (HR^+) disease received adjuvant endocrine therapy. After completion of local therapy, adjuvant trastuzumab was administered every 3 weeks for up to 1 year. The patients with HR^+ breast cancer received adjuvant trastuzumab in combination with endocrine therapy.

Figure 1 Study Regimen



Study Evaluation and Criteria

The HER2 status of a CNB was determined by immunohistochemistry and/or fluorescence in situ hybridization performed in each institution (no central review) before study enrollment. After completion of PST, resected specimens and CNB specimens were evaluated centrally by 3 breast pathologists (H.T., F.A. and M.K.). The pCR was defined as the absence of viable invasive tumor in both the breast and the axillary nodes. Patients with residual ductal carcinoma in situ (DCIS) in breast tissue and no viable invasive tumor in the axillary nodes also were classified as having pCR. Clinical response was evaluated by palpation after each cycle by using the response evaluation criteria in solid tumors.[25]

All adverse events were evaluated according to the CTCAE (Common Terminology Criteria for Adverse Events) v3.0.[26] Infusion reactions were defined by the occurrence of the following symptoms during infusion or within 24 hours after starting trastuzumab: pyrexia, chills, nausea, vomiting, pain, headache, cough, dyspnea, dizziness, rash, pruritus, general malaise, skin eruption, and decrease in blood pressure.

Endpoints and Statistical Analysis

The primary endpoint was the pCR rate. The secondary endpoints were disease-free survival, clinical response rate, breast conservation rate, and safety. In this report, disease-free survival is not reported because of the short follow-up. Analyses of efficacy and safety were performed in the intent-to-treat (ITT) population. The ITT population comprised subjects fulfilling the study inclusion criteria who had received at least one dose of study chemotherapy. The per-protocol population comprised ITT subjects who had undergone surgery in this study without serious violations of the inclusion criteria. As sensitivity analysis, the pCR rates among the per-protocol population were calculated. By assuming a difference in the pCR rate between the 2 groups of 10% and an expected baseline pCR rate of 30%, a sample size of 49 patients in each treatment group was necessary to demonstrate a higher pCR rate with a probability of 85%. The target number of patients was considered to be 100 patients to allow for patient dropout. The pCR was compared between 2 groups by using the χ^2 test. P values $<.05$ were considered statistically significant.

Results

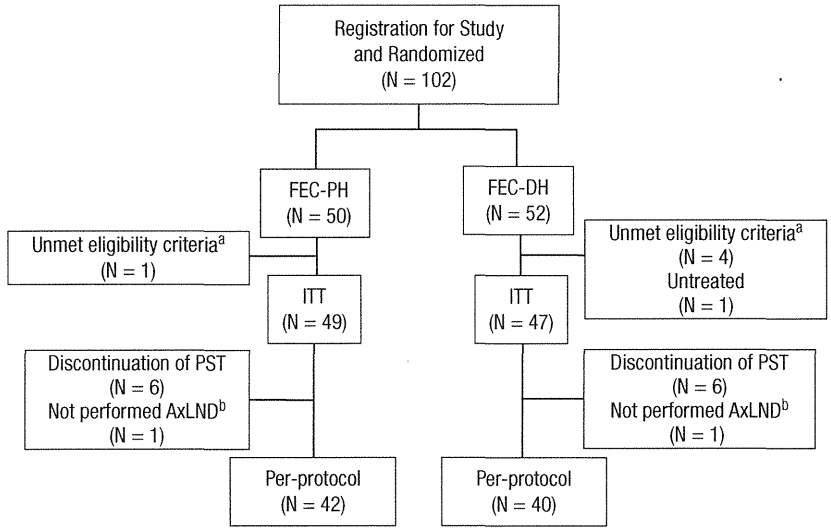
Patient Characteristics

Between March 2007 and June 2008, 102 patients were enrolled in this study. Of these, 49 patients receiving FEC-PH and 47 receiving FEC-DH were evaluable in the ITT population. According to central review, 4 patients were considered ineligible (2 patients not $HER2^+$, 1 not evaluable for HER2 status, 1 with noninvasive carcinoma in the CNB specimen). One patient had an aneurysm of the thoracic aorta immediately after the first cycle of FEC, discontinued FEC, and, therefore, was considered ineligible. One patient did not receive PST because of persistent hypertension (Figure 2).

The characteristics of the ITT population are shown in Table 1. Distribution of tumor size was similar in the 2 treatment groups. The proportion of patients with clinically diagnosed axillary node-positive tumors was higher in the FEC-DH arm. Approximately two-thirds of patients had HR^- tumors, with a slightly higher representation in the FEC-DH than in the FEC-PH arm.

One patient in the FEC-DH arm was considered not evaluable for pathologic response by central review because she had not undergone AxLND or SNLB before PST and had DCIS in the breast after surgery. Eighty-four patients received surgery after completion of PST. The HR and HER2 status of the breast tumors were not reassessed after surgery. Twelve of 72 patients who received AxLND had lymph-node metastases. Two patients did not undergo either AxLND or SLNB before PST. Therefore, 82

Figure 2 Consort Diagram



[a]Three Cases Were Human Epidermal Growth Factor Receptor 2 Negative (HER2$^-$) by Central Review. [b]Axillary Node Dissection.

patients (42 in the FEC-PH arm and 40 in the FEC-DH arm) were evaluated in the per-protocol population (Figure 2).

Treatment Exposure

Ninety-one (94.8%) of 96 patients completed 4 cycles of FEC. Four patients discontinued FEC due to adverse events, and one patient discontinued due to disease progression after 2 cycles of FEC. Among patients who completed 4 cycles of FEC, 3 discontinued PH (grade 3 neurotoxicity in 2 patients; suicide in 1 patient) and 4 discontinued DH (adverse events in 2 patients; disease progression after 1 cycle in 1 patient; refusal in one patient). Thus, 43 of 49 patients (87.8%) in the FEC-PH arm and 41 (87.2%) of 47 patients in the FEC-DH arm completed PST.

Efficacy

In the ITT population, 23 (46.9%) of 49 patients receiving FEC-PH and 21 (44.7%) of 47 patients receiving FEC-DH achieved a pCR according to central pathologic review. The difference between FEC-PH and FEC-DH is 2.3% (95% confidence interval [CI], −17.7% to 22.2%; $P = .82$). The pCR rates were 54.8% with FEC-PH and 50.0% with FEC-DH in the per-protocol population. The difference is 4.8% (95% CI, −16.8% to 26.4%; $P = .67$). The difference between the 2 arms were <10%. The pCR rate included 24 patients with DCIS in the breast (10 in the FEC-PH arm and 14 in the FEC-DH arm). No patients with pCR in the breast had persistent nodal carcinoma. The pCR rates according to institutional review were 44.9% (22/49) in the FEC-PH arm and 36.2% (17/47) in the FEC-DH arm; 4 patients who were diagnosed with residual invasive carcinoma in the breast by institutional review were assessed as pCR with DCIS by central review.

Subpopulation analysis according to HR status showed pCR rates of 54.2% (32/59) in HR$^-$ tumors and 29.7% (11/37) in HR$^+$ tumors ($P = .02$). The pCR rates in patients with HR$^+$ tumors were 26.1% with FEC-PH and 35.7% with FEC-DH ($P = .54$) (Figure 3). In patients with HR$^-$ tumors, the pCR rates for FEC-PH and FEC-DH were 65.4% and 45.5%, respectively ($P = .13$) (Figure 3). The clinical response rates by palpation were 79.6% in the FEC-PH arm and 76.6% in the FEC-DH arm, respectively (Table 2). Eighty-four patients received surgery. Seventy-two of these 84 patients received adjuvant trastuzumab. BCT was possible in 35 patients (71.4%) in the FEC-PH arm and 27 (57.4%) in the FEC-DH arm.

Safety

Grade 3/4 neutropenia was observed in 28.1% of 96 patients who received FEC, and 11 patients (11.5%) developed febrile neutropenia (Table 3). Adverse events that lead to hospitalization were reported in a total of 8 patients during FEC; 3 of these discontinued FEC. During the taxane phase, peripheral neurotoxicity was more common with PH than DH, whereas grade 3/4 neutropenia, febrile neutropenia, peripheral edema, and grade 1/2 mucositis and/or stomatitis were more common with DH than with PH. One patient developed grade 3 peripheral edema after 2 cycles of DH and stopped chemotherapy.

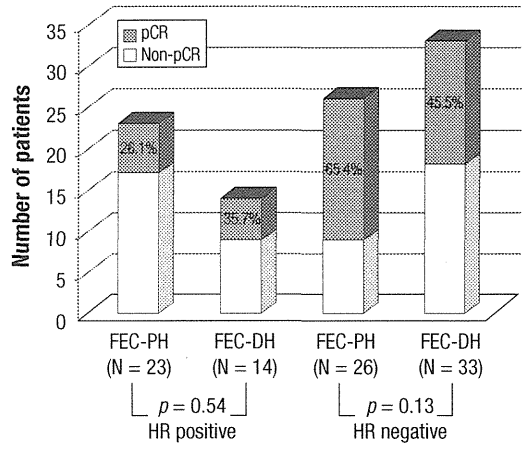
Cardiac events were observed in 4 patients. Two patients who received PH and 1 patient who received DH experienced grade 1 supraventricular arrhythmia. One patient developed grade 3 left ventricular systolic dysfunction with shortness of breath on exertion immediately after completion of 4 cycles of PH, accompanied by a decrease in LVEF to 39%. She had no history of cardiovascular disease but had received diuretic and beta-blocker

Table 1 Patient Characteristics

	FEC-PH (n = 49)	FEC-DH (n = 47)
Median Age (Range), y	51 (34-65)	53 (28-63)
Clinical Stage, No. (%) Patients		
IIA[a]	21 (42.9)	16 (34.0)
IIB	19 (38.8)	22 (46.8)
IIIA	9 (18.4)	9 (19.1)
Tumor, No. (%) Patients		
T1	1 (2.0)	1 (2.1)
T2	38 (77.6)	34 (72.3)
T3	10 (20.4)	12 (25.6)
Axillary Lymph Node-Positive Determination, No. (%) Patients		
Ultrasonography	27 (55.1)	33 (70.2)
SLNB	5 (10.2)	2 (4.3)
HER2 Status, No. (%) Patients		
IHC 3+	43 (87.8)	43 (91.5)
IHC 2+/FISH +	6 (12.2)	4 (8.5)
Hormone Receptor Status No. (%) Patients		
ER+/PgR+	12 (24.5)	4 (8.5)
ER+/PgR−	1 (20.4)	10 (21.3)
ER−/PgR+	1 (2.0)	0 (0)
ER−/PgR−	26 (53.1)	33 (70.2)

Abbreviations: DH = docetaxel; ER = estrogen receptor; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PgR = progesterone receptor; PH = paclitaxel; SLNB =sentinel lymph node biopsy.
[a] Including patients with tumor 2 cm in greatest dimension (T1c) and N0.

Figure 3 Pathologic Results According to Hormone Receptor (HR) Status. The Left Side Shows Pathologic Complete Response (pCR) in Patients With HR+ Disease and the Right Side Shows pCR in Those With HR− Disease



therapy for left ventricular systolic dysfunction. After 2 months, her symptoms had resolved with treatment, and she underwent BCT. Her LVEF had recovered to 58% one year after completion of PST. Four patients with adverse events were hospitalized during the trastuzumab plus taxane phase (1 patient received PH and 3 received DH). All remaining 84 patients who completed PST underwent surgery.

Twenty-nine (31.9%) of 91 patients who received trastuzumab plus taxane experienced infusion reactions during the first cycle of trastuzumab (14 patients with PH and 15 with DH). Among patients with infusion reactions, rigors and/or chills, fever, and pain were commonly observed; all events were grade 1 or 2. Eight (27.6%; 8.8% of all patients receiving trastuzumab plus taxane) of 29 patients who experienced infusion reactions during the first cycle of trastuzumab experienced a further infusion reaction during a later cycle.

Discussion

This study showed high pCR rates (46.9% with FEC-PH and 42.6% with FEC-DH) and that 62 (73.8%) of 84 patients undergoing surgery were able to receive BCT. The results of this study are consistent with the high pCR rates reported in previous trials that evaluated the combination of chemotherapy and trastuzumab as PST.[13-20,27] However, there was no significant difference in pCR rates between the 2 treatment groups. There was a trend to a higher rate of BCT with FEC-PH compared with FEC-DH, but the difference was not statistically significant. The small sample size may explain the lack of significant difference between the regimens.

The pCR rates were significantly higher in HR^- tumors than in HR^+ tumors with both treatments. This result is consistent with findings from several other studies of trastuzumab combined with anthracycline- and nonanthracyline-based regimens, including NOAH (concurrent anthracycline/taxane)[14] NeoSphere (docetaxel),[28] and NeoALTTO (paclitaxel).[29] Analysis of the data from these studies suggests that patients with $HER2^+$ and HR^- disease will obtain greatest benefit from a trastuzumab-containing chemotherapeutic regimen. Although other findings, reported by Peintinger et al[30] and Buzdar et al[13] contrast with results from NOAH, NeoSphere, NeoALTTO and the present study, the larger studies have demonstrated higher pCR rates in HR^- than HR^+ breast cancer after trastuzumab-based regimens. Moreover, after the initial conclusions from Buzdar[13] and Peintinger,[30] additional data from the M.D. Anderson group demonstrated a statistically higher pCR rate in HR^- than HR^+ breast cancer (61.1% vs. 38.9%, respectively). Recently, von Minckwitz et al[31] presented data from a meta-analysis of 7 trials (n = 6377) of neoadjuvant therapy, including anthracyclines and taxanes with or without trastuzumab, that showed that pCR is a surrogate for survival in patients with HER2+ HR^- breast cancer but not in those with HR^+ disease. It is also relevant to note that, in large trials of adjuvant therapy, prognosis is not different between HR^- and HR^- tumors.[8-10] Therefore, longer follow-up is required in the setting of PST before definitive conclusions can be made about the importance of HR status and therapeutic outcomes. Further clinical and translational